TENT COOPERATION TRE

РСТ	From the INTERNATIONAL BUREAU			
NOTIFICATION OF ELECTION (PCT Rule 61.2) Date of mailing (day/month/year) 28 September 2000 (28.09.00)	Assistant Commissioner for Patents United States Patent and Trademark Office Box PCT Washington, D.C.20231 ETATS-UNIS D'AMERIQUE			
International application No. PCT/US00/00284	Applicant's or agent's file reference 14028.0293/P			
International filing date (day/month/year) .06 January 2000 (06.01.00) .Applicant	Priority date (day/month/year) 08 January 1999 (08.01.99)			
KNECHTLE, Stuart, J. et al				
in the demand filed with the International Preliminary 07 August 2000 in a notice effecting later election filed with the International Preliminary	0 (07.08.00)			
2. The election X was was was not was not made before the expiration of 19 months from the priority date Rule 32.2(b).	e or where Pulo 22 and in the same			
Rule 32.2(b).	and of applies, within the time limit under			

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35

Authorized officer

Maria Kirchner

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

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REC'D	11	APR	2001
MAPO			~ · · · · · · · · · · · · · · · · · · ·

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's 14028.02	or agent's file reference	FOR FURTHER ACTIO		ation of Transmittal of International Examination Report (Form PCT/IPEA/416)		
Internationa	application No.	International filing date (day/mo	onth/year)	Priority date (day/month/year)		
PCT/USC	00/00284	06/01/2000		08/01/1999		
	International Patent Classification (IPC) or national classification and IPC A61K47/48					
Applicant						
WISCON	SIN ALUMNI RESEARCH	FOUNDATION et al.				
and is	1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.					
2. IIIIS F	EPORT consists of a total of	8 sneets, including this cove	r sneet.			
be	nis report is also accompanied een amended and are the bas ee Rule 70.16 and Section 60	is for this report and/or sheet	s containing red	n, claims and/or drawings which have ctifications made before this Authority e PCT).		
These	annexes consist of a total of	sheets.				
3. This re	eport contains indications relat	ing to the following items:				
ı	☑ Basis of the report			İ		
11	☐ Priority .					
111	_	pinion with regard to novelty,	nventive step a	and industrial applicability		
IV	☐ Lack of unity of invention					
V	Reasoned statement un citations and explanation	der Article 35(2) with regard t ns suporting such statement	o novelty, invei	ntive step or industrial applicability;		
VI	☐ Certain documents cite					
VII	☑ Certain defects in the int					
VIII	☐ Certain observations on the international application					
Date of subm	nission of the demand	Date	of completion of the	nis report		
07/08/200	07/08/2000 09.04.2001					
Name and mailing address of the international preliminary examining authority: Authorized officer			Santon Santon			

Bochelen, D

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D-80298 Munich

International application No. PCT/US00/00284

I.	Ba	sis of the report				
1.	1. With regard to the elements of the international application (Replacement sheets which have been furnishing the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally for and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)): Description, pages:					
	1-3	as originally filed				
	Cla	aims, No.:				
	1-3	as originally filed				
2.	Wit lan	h regard to the language , all the elements marked above were available or furnished to this Authority in the guage in which the international application was filed, unless otherwise indicated under this item.				
	The	ese elements were available or furnished to this Authority in the following language: , which is:				
		the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).				
		the language of publication of the international application (under Rule 48.3(b)).				
		the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).				
3.	Wit inte	h regard to any nucleotide and/or amino acid sequence disclosed in the international application, the rnational preliminary examination was carried out on the basis of the sequence listing:				
		contained in the international application in written form.				
		filed together with the international application in computer readable form.				

listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ furnished subsequently to this Authority in written form.

furnished subsequently to this Authority in computer readable form.

the international application as filed has been furnished.

the description,	pages:
the claims,	Nos.:
the drawings,	sheets:

5. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in

☐ The statement that the information recorded in computer readable form is identical to the written sequence

International application No. PCT/US00/00284

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6.	Add	ditional observations, if r	necessa	ıry:					
Ш	. No	n-establishment of opi	nion wi	th regard	i to novelty,	inventive st	ep and indus	trial applica	bility
	The	e questions whether the rious), or to be industrial	claimed	l inventio	n appears to I	be novel, to i	nvolve an inve		-
		the entire international					•		
	×	claims Nos. 1-33 with r	espect	to industr	ial applicabilit	ty.			
be	ecaus	se:							
	×	the said international a does not require an inte see separate sheet	pplication ernation	on, or the al prelimi	said claims N nary examina	los. 1-33 relation (<i>specify</i>	ate to the follow):	wing subject	matter which
		the description, claims that no meaningful opin	or draw iion cou	ings (<i>indi</i> ld be forr	cate particula ned (specify):	ar elements b	<i>pelow</i>) or said o	claims Nos.	are so unclear
		the claims, or said clain could be formed.	ns Nos.	are so ir	nadequately s	supported by	the description	n that no me	aningful opinior
		no international search	report h	nas been	established fo	or the said cl	aims Nos		
2.	and	eaningful international p for amino acid sequence ructions:	relimina e listing	ary exami to comply	nation cannot with the star	t be carried o	out due to the f ed for in Anne	ailure of the	nucleotide Iministrative
		the written form has not	been fu	urnished	or does not co	omply with th	ie standard.		
		the computer readable	form ha	s not bee	n furnished o	r does not co	omply with the	standard.	
V.	Rea citat	soned statement unde tions and explanations	r Article suppo	e 35(2) w rting suc	ith regard to th statement	novelty, inv	entive step o	r industrial	applicability;
1.	State	ement							
	Nove	elty (N)	Yes: No:	Claims Claims	1-33				
	Inve	ntive step (IS)	Yes: No:	Claims Claims	1-33				
	Indu	strial applicability (IA)	Yes:	Claims	see separate	e sheet			

International application No. PCT/US00/00284

No: Claims

2. Citations and explanations see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-33 relate to subject-matter considered by this Authority to be covered by 1. the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: KOULMANDA M ET AL: 'Cyclophosphamide, but not CTLA4Ig, prolongs survival of fetal pig islet grafts in anti-T cell monoclonal antibody-treated NOD mice.' XENOTRANSPLANTATION (1998) 5 215-21 , XP000915296
- D2: WO 98 52606 A (BIOGEN) 26 November 1998 (1998-11-26)
- D3: WO 96 32137 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 17 October 1996 (1996-10-17)
- D4: WO 99 53954 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 28 October 1999 (1999-10-28)
- D5: WO 98 56417 A (THE UNITED STATES OF AMERICA) 17 December 1998 (1998-12-17)
- D6: WO 98 39363 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 11 September 1998 (1998-09-11)
- D7: WO 95 34320 A (REGENTS OF THE UNIVERSITY OF MINNESOTA) 21 December 1995 (1995-12-21)

2. Novelty (Art. 33 (1) and (2) PCT):

The prior art discloses methods to prevent graft rejection by using either inhibitors of T-cell co-stimulation, e.g. CTLA4-Ig (D1: p218 col1 §3; D5: p14 I21; D7: abstract.

claim 7), 5c8 (D2: claim 5), anti-B7 antibody (D7: claim 8), or by reducing the T-cell population with immunotoxins (D3: claims 1, 7; D4: claims 1, 8; D6: claims 1, 27). Document D1 discloses the use of a combination of anti-CD3 or anti-CD4 antibodies and inhibitors of T cell co-stimulation (D1: p218 col2 §2) in order to prevent graft rejection. The subject-matter of claims 1-28 differs in that a combination of immunotoxins with inhibitors of the co-stimulation are proposed to prevent graft rejection. Therefore, the subject-matter of claims 1-28 appears to be new.

The subject-matter of claims 29-33 is considered to be new. The prior art discloses the use of immunotoxins to induce immune tolerance by reducing T-cell population and thus to prevent acute graft rejection in the peritransplant period (D3: p18 I7; D4: p9 I10). The subject-matter of claims 29-23 differs in that the immunotoxins are administered after transplantation when rejection occurs.

3. Inventive step (Art. 33 (1) and (3) PCT):

The subject-matter of claims 1-28 does not involve an inventive step for the following reasons.

Document D1, which is considered to be the closest prior art, discloses the combination of anti-CD3 or anti-CD4 antibodies that deplete the T-cell population (D1: abstract, p218 fig3), with an inhibitor of the co-stimulation of T-cells, i.e. CTLA4Ig, in order to prevent graft rejection. The problem underlying the application is therefore to find an alternative method to prevent graft rejection. The solution proposed is to combine co-stimulation blockers with immunotoxins. The prior art discloses the use of immunotoxins, e.g. UCHT1-CRM9 (D4: claim 8) in order to reduce the population of T-cells (D3: claim 1; D4: claim 1) and to prevent graft rejection. Therefore, it would be obvious for a man skilled in the art to use immunotoxins in combination with co-stimulation blockers in order to prevent graft rejection. Moreover, immunotoxins as well as co-stimulation blockers per se are known for their use to prevent graft rejection (see item 2.). The combination of known pharmaceutical compounds in order to obtain the same therapeutical effect as the compounds per se, involves an inventive step only if there is an unexpected advantage over the prior art. The application does not provide any evidence of such an advantage.

Immunotoxins are known for inducing immune tolerance by reducing T-cell

population in the peritransplantation period (D3: p18 l7; D4: p9 l10) The subjectmatter of claims 29-33 differs in that immunotoxin treatment is administered when signs of rejection are detected. It would be obvious for a skilled man to administer the same treatment as used for inducing immune tolerance, in order to reverse the late acute graft rejection by reducing T-cell population. Therefore, the subject- matter of claims 29-33 does not involve an inventive step.

4. Industrial applicability (Art (1) and (4) PCT):

For the assessment of the present claims 1-33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

- The units of measure employed on page 17 are not additionally expressed in terms 5. of the units stipulated by Rule 10.1 (a) PCT.
- The units used on page 20 line 4 and page 24 line 9 are not consistent contrary to 6. the requirement of Rule 10 (2) PCT.

Re Item VIII

Certain observations on the international application

- The embodiment of the invention described on page 21 does not fall within the scope 7. of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- In claims 29-33, the step of monitoring the recipient for signs of rejection is not 8.

INTERNATIONAL PRELIMINARY **EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/00284

considered to be a characterizing technical feature since it is a standard procedure following transplantation.

F NT COOPERATION TREATY



INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER see Notification of Transmittal of International Search Report				
14028.0293/P	ACTION (Form PCT/ISA/220) as well as, where applicable, item 5 below.				
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)			
PCT/US 00/00284	06/01/2000	08/01/1999			
Applicant					
WISONSIN ALUMNI RESEARCH I	FOUNDATION et al.				
This International Search Report has been according to Article 18. A copy is being tra	n prepared by this International Searching Auth	nority and is transmitted to the applicant			
This International Search Report consists					
X It is also accompanied by	a copy of each prior art document cited in this	report.			
Basis of the report					
a. With regard to the language, the i	nternational search was carried out on the bases otherwise indicated under this item.	sis of the international application in the			
the international search was Authority (Rule 23.1(b)).	as carried out on the basis of a translation of the	ne international application furnished to this			
 b. With regard to any nucleotide and was carried out on the basis of the 	dor amino acid sequence disclosed in the in	ternational application, the international search			
J	nal application in written form.				
filed together with the inter	rnational application in computer readable form	n.			
furnished subsequently to	this Authority in written form.				
furnished subsequently to this Authority in computer readble form.					
the statement that the sub- international application as	sequently furnished written sequence listing do s filed has been furnished.	pes not go beyond the disclosure in the			
the statement that the infor	rmation recorded in computer readable form is	identical to the written sequence listing has been			
2. X Certain claims were foun	ed umasarahahla (Cas Bau I)				
3. Unity of invention is lack	d unsearchable (See Box I).				
only of invention is lack	ing (see box ii).				
4. With regard to the title.					
the text is approved as sub	omitted by the applicant				
	ed by this Authority to read as follows:				
	,				
5. With regard to the abstract,	•				
the text is approved as sub the text has been establish within one month from the	mitted by the applicant. ed, according to Rule 38.2(b), by this Authority date of mailing of this international search repo	y as it appears in Box III. The applicant may, ort, submit comments to this Authority.			
6. The figure of the drawings to be publis	shed with the abstract is Figure No.				
as suggested by the applic	-	None of the figures.			
because the applicant faile	d to suggest a figure.				
because this figure better o	haracterizes the invention.				
		· · · · · · · · · · · · · · · · · · ·			



Relevant to claim No.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61K39/395 A61K38/17 A61K38/13 A61K31/4353
A61K31/52 A61K31/56 //(A61K47/48,39:395),(A61K47/48,38:17),
(A61K47/48,38:13),(A61K47/48,31:4353),(A61K47/48,31:52),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Citation of document, with indication, where appropriate, of the relevant passages

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

X	KOULMANDA M ET AL: "Cyclophosp not CTLA4Ig, prolongs survival pig islet grafts in anti-T cell antibody-treated NOD mice." XENOTRANSPLANTATION (1998) 5 21 XP000915296 abstract	of fetal monoclonal	1-6, 11-13
Y	WO 98 52606 A (BIOGEN) 26 November 1998 (1998-11-26) claims 1-28		1-33
Y	WO 96 32137 A (THE GOVERNMENT O UNITED STATES OF AMERICA) 17 October 1996 (1996–10–17) claims 1–38	F THE -/	1-33
	her documents are listed in the continuation of box C. tegories of cited documents:	Patent family members are listed "T" later document published after the inte	
consid "E" earlier of filing d "L" docume which citation "O" docume other r "P" docume	ent defining the general state of the art which is not lered to be of particular relevance document but published on or after the international late that which may throw doubts on priority claim(s) or is cited to establish the publication date of another nor other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but nan the priority date claimed	or priority date and not in conflict with cited to understand the principle or the invention "X" document of particular relevance; the c cannot be considered novel or cannot involve an inventive step when the do "Y" document of particular relevance; the c cannot be considered to involve an in the art. "&" document member of the same patent	the application but sory underlying the laimed invention be considered to coment is taken, alone laimed invention ventive step when the re other such decursion as person skilled
	actual completion of the international search 0 July 2000	Date of mailing of the international sea	rch report
Name and n	nailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Le Flao, K	

Interestional Application No Pt S 00/00284

A. CLASS IPC 7	ification of subject matter (A61K47/48,31:56)	•	•		
	· · · · · · · · · · · · · · · · · · ·				
According t	o International Patent Classification (IPC) or to both national classifi	cation and IPC			
B. FIELDS	SEARCHED	<u> </u>	·		
Minimum d	ocumentation searched (classification system followed by classifica-	tion symbols)			
<u>.</u>					
Documenta	tion searched other than minimum documentation to the extent that	such documents are included in the fields s	earched		
Electronic o	lata base consulted during the international search (name of data b	pase and, where practical, search terms used	(t		
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		T		
Category °	Citation of document, with indication, where appropriate, of the re	elevant passages	Relevant to claim No.		
Α	WO 99 53954 A (THE GOVERNMENT OF UNITED STATES OF AMERICA)	THE	10		
	28 October 1999 (1999-10-28)		·		
	claim 8				
Α	WO 98 56417 A (THE UNITED STATES		1-33		
	AMERICA) 17 December 1998 (1998- claims 1-16	12-17)			
Α	WO 98 39363 A (THE GOVERNMENT OF	THE	1-33		
	UNITED STATES OF AMERICA) 11 September 1998 (1998-09-11)				
	claims 1-42				
Α	WO 95 34320 A (REGENTS OF THE UN	IVERSITY	1 .		
	OF MINNESOTA)				
	21 December 1995 (1995-12-21) claims 1-77		·		
	L				
Funt	her documents are listed in the continuation of box C.	Patent family members are listed	in annex.		
° Special ca	tegories of cited documents:	"T" later document published after the inte			
	ent defining the general state of the art which is not lered to be of particular relevance	or priority date and not in conflict with cited to understand the principle or th			
"E" earlier o	"E" earlier document but published on or after the international "X" document of particular relevance; the claimed invention				
filling date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another "L" document of particular relevance; the claimed invention involve an inventive step when the document is taken alone					
citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or "O" document referring to an oral disclosure, use, exhibition or					
"P" docume					
	actual completion of the international search	*8* document member of the same patent Date of mailing of the international sec			
1	0 July 2000				
		Authorized officer			
тапе ало п	nailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2	Authorized officer	•		
	NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Le Flao, K			

1

Inform

on patent family members

Interpretable Application No
PCS 00/00284

				00/00264
Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WQ 9852606 A	26-11-1998	AU 74940	98 A	11-12-1998
		EP 09802		23-02-2000
		NO 9956		17-01-2000
		AU 79567		30-12-1998
•		EP 10094		21-06-2000
		W0 98564		17-12-1998
WO 9632137 A	17-10-1996	AU 56637	 96 А	30-10-1996
	•	CA 22181	66 A	17-10-1996
	•	EP 083014	46 A	25-03-1998
		US 576292	27 A	09-06-1998
W0 9953954 A	28-10-1999	AU 365449	99 A	08-11-1999
WO 9856417 A	17-12-1998	AU 749409	 98 A	11-12-1998
	•	AU 795679		30-12-1998
	•	EP 098025		23-02-2000
	• _	EP 100943		21-06-2000
		NO 99561		17-01-2000
	- -	WO 985260		26-11-1998
WO 9839363 A	11-09-1998	AU 654269	8 A	22-09-1998
		EP 101549		05-07-2000
WO 9534320 A	21-12-1995	AU 270189		
		CA 219173		05-01-1996
		EP 078448		21-12-1995
		JP 1050181		23-07-1997 17-02-1998



. From the INTERNATIONAL SEARCHING AUTHORITY	DOT			
То:	PCT			
NEEDLE & ROSENBERG, P.C.	NOTIFICATION OF TRANSMITTAL OF			
Suite 1200 Attn. SPRATT, G.	THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION			
The Candler Building	EIVED OR THE DECLARATION			
127 Peachtree Street, N.E. Atlanta, GA 30303-1811 JUL	1 2000 (PCT Rule 44.1)			
INITED CALL	ROSENBERG			
NELDES				
·	Date of mailing (day/month/year) 25/07/2000			
Applicant's or agent's file reference	23/01/2000			
14028.0293/P	FOR FURTHER ACTION See paragraphs 1 and 4 below			
International application No. PCT/US 00/00284	International filing date (day/month/year) OC IO 1 IO OO			
Applicant	06/01/2000			
LITCONCIN ALLIMANT DECEMBER -				
WISONSIN ALUMNI RESEARCH FOUNDATION et a	1.			
1. X The applicant is hereby notified that the International Search	Popost has been excluded			
Filling of amendments and statement under Article 19:				
The applicant is entitled, if he so wishes, to amend the claims				
When? The time limit for filing such amendments is normall International Search Report; however, for more details	y 2 months from the date of transmittal of the ails, see the notes on the accompanying sheet			
Where? Directly to the International Bureau of WIPO	DOS/TWM/TON			
34, chemin des Colombettes 1211 Geneva 20, Switzerland	DOCKETED /			
Fascimile No.: (41-22) 740.14.35 For more detailed instructions, see the notes on the accom	800 Date 7/31/00			
	UGAIGMSD:			
 The applicant is hereby notified that no International Search F Article 17(2)(a) to that effect is transmitted herewith. 	Report will be established and that the declaration under			
With regard to the protest against payment of (an) additiona	al fee(s) under Rule 40.2, the applicant is notified that:			
the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.				
no decision has been made yet on the protest; the application	ant will be notified as soon as a decision is made.			
Further action(s): The applicant is reminded of the following:				
Shortly after 18 months from the priority data, the international and international				
priority claim, must reach the International Burgon to publication, a robotic of whiternational application, or of the				
. , and the international publication	''·			
Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).				
Within 20 months from the priority date, the applicant must and any				
before all designated Offices which have not been elected in the de priority date or could not be elected because they are not bound by	emand or in a later election within 19 months from the Chapter II.			

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016

Authorized officer

Catherine Humbert

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been his filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

Notes to Form PCT/ISA/220 (first sheet) (January 1994)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

- [Where originally there were 48 claims and after amendment of some claims there are 51]:
 Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added.
- [Where originally there were 15 claims and after amendment of all claims there are 11]: "Claims 1 to 15 replaced by amended claims 1 to 11."
- [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
 "Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or "Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
- [Where various kinds of amendments are made]:
 "Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.



(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.				
14028.0293/P	ACTION				
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)			
PCT/US 00/00284	06/01/2000	08/01/1999			
Applicant					
	•				
WISONSIN ALUMNI RESEARCH	FOUNDATION et al.				
according to Article 18. A copy is being tra		ority and is transmitted to the applicant			
This International Search Report consists It is also accompanied by	of a total of4 sheets. a copy of each prior art document cited in this	report.			
Basis of the report With report to the lenguage the i	nternational search was carried out on the bas	ic of the international application in the			
	ess otherwise indicated under this item.	is of the international application in the			
the international search was Authority (Rule 23.1(b)).	as carried out on the basis of a translation of th	ne international application furnished to this			
b. With regard to any nucleotide and was carried out on the basis of the	sequence listing:	ternational application, the international search			
. =	nal application in written form.				
I 😕	national application in computer readable form this Authority in written form.	ı.			
	this Authority in computer readble form.	•			
	sequently furnished written sequence listing do	pes not go beyond the disclosure in the			
international application as	s filed has been furnished.				
the statement that the information furnished	rmation recorded in computer readable form is	identical to the written sequence listing has been			
2. X Certain claims were foun	d unsearchable (See Box I).				
3. Unity of Invention is lack	Ing (see Box II).				
		•			
4. With regard to the title,					
the text is approved as sub	• • • • • • • • • • • • • • • • • • • •				
the text has been established by this Authority to read as follows:					
-					
5. With regard to the abstract,					
the text is approved as sub					
	ed, according to Rule 38.2(b), by this Authority date of mailing of this international search repo				
6. The figure of the drawings to be publis	shed with the abstract is Figure No.				
as suggested by the applic	ant.	None of the figures.			
because the applicant faile	d to suggest a figure.				
because this figure better of	haracterizes the invention.	•			
L. 	·· ···································				



Relevant to claim No.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K47/48 A61K39/395 A61K38/17 A61K38/13 A61K31/4353 //(A61K47/48,39:395),(A61K47/48,38:17), A61K31/52 A61K31/56

(A61K47/48, 38:13), (A61K47/48, 31:4353), (A61K47/48, 31:52),According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Minimum documentation searched (classification system followed by classification symbols) IPC 7-A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

Citation of document, with indication, where appropriate, of the relevant passages

EPO-Internal, WPI Data, PAJ, MEDLINE, BIOSIS, CHEM ABS Data, EMBASE

			l
X	KOULMANDA M ET AL: "Cyclophos not CTLA4Ig, prolongs survival pig islet grafts in anti-T cel antibody-treated NOD mice." XENOTRANSPLANTATION (1998) 5 2 XP000915296 abstract	of fetal l monoclonal	1-6, 11-13
Y	WO 98 52606 A (BIOGEN) 26 November 1998 (1998-11-26) claims 1-28		1-33
Υ	WO 96 32137 A (THE GOVERNMENT UNITED STATES OF AMERICA) 17 October 1996 (1996-10-17) claims 1-38	OF THE	1–33
	·	-/	
X Furt	ther documents are listed in the continuation of box C.	Patent family members are listed	in annex.
"A" docume consider filing of "L" docume which citation others "P" docume "P" docume	ent defining the general state of the art which is not dered to be of particular relevance document but published on or after the international date ent which may throw doubts on priority claim(s) or is cited to establish the publication date of another or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or means ent published prior to the international filing date but than the priority date claimed	"T" later document published after the inte or priority date and not in conflict with cited to understand the principle or the invention "X" document of particular relevance; the c cannot be considered novel or cannot involve an inventive step when the document of particular relevance; the c cannot be considered to involve an inventive step when the document is combined with one or mo ments, such combination being obvious in the art. "&" document member of the same patent to	the application but every underlying the laimed invention be considered to cument is taken alone laimed invention ventive step when the re other such docu- us to a person skilled
Date of the	actual completion of the international search	Date of mailing of the international sea	rch report
1	0 July 2000	25/07/2000	
Name and r	mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Le Flao, K	
orm PCT/ISA/2	210 (second sheet) (July 1992)		
		nage 1 of	2

1





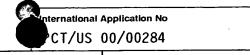
A: CLASS IPC 7	ification of subject matter (A61K47/48, 31:56)		
According	to International Patent Classification (IPC) or to both national classific	eation and IPC	
	SEARCHED		
Minimum d	ocumentation searched (classification system followed by classificati	ion symbols)	
	ation searched other than minimum documentation to the extent that ${f s}$	·	
Electronic o	data base consulted during the international search (name of data ba	ise and, where practical, search terms used	
	·		
C. DOCUM	ENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the rel	evant passages	Relevant to claim No.
A	WO 99 53954 A (THE GOVERNMENT OF UNITED STATES OF AMERICA) 28 October 1999 (1999-10-28)	THE	10
	claim 8		
Α	WO 98 56417 A (THE UNITED STATES AMERICA) 17 December 1998 (1998-1 claims 1-16		1-33
Α	WO 98 39363 A (THE GOVERNMENT OF UNITED STATES OF AMERICA) 11 September 1998 (1998-09-11) claims 1-42	THE	1-33
А	WO 95 34320 A (REGENTS OF THE UNI OF MINNESOTA) 21 December 1995 (1995-12-21) claims 1-77	VERSITY	1
Furti	her documents are listed in the continuation of box C.	χ Patent family members are listed in	n annex.
° Special ca	tegories of cited documents :	The designant muhlished after the inter	
consid "E" earlier o	ent defining the general state of the art which is not lered to be of particular relevance document but published on or after the international	"T" later document published after the inter or priority date and not in conflict with t cited to understand the principle or the invention "X" document of particular relevance; the clause	the application but ory underlying the
filing d		cannot be considered novel or cannot linvolve an inventive step when the doc	be considered to
which in citation "O" docume	is cited to establish the publication date of another n or other special reason (as specified) ent referring to an oral disclosure, use, exhibition or	"Y" document of particular relevance; the cla cannot be considered to involve an inv document is combined with one or mor	aimed invention entive step when the re other such docu-
other n	neans ent published prior to the international filing date but	ments, such combination being obvious in the art. "&" document member of the same patent factors.	•
	actual completion of the international search	Date of mailing of the international sear	
1(0 July 2000		·
Name and m	nailing address of the ISA	Authorized officer	
	European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fay: (+31-70) 340-3016	Le Flao, K	

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
R mark on Protest The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

mation on patent family members



•								
	tent document in search report		Publication date		Patent family member(s)	_	Publication date	
МО	9852606	Α	26-11-1998	AU	7494098	Α	11-12-1998	
WU	9032000	^	20 11 1550	EP	0980259		23-02-2000	
				NO		Α	17-01-2000	
				AU	7956798	A	30-12-1998	
				EP	1009432		21-06-2000	
				WO	9856417	Α	17-12-1998	
WO	9632137		17-10-1996	AU	5663796	A	30-10-1996	
	3002107	••	2.7 2.5 2.2.2.	CA	2218166	Α	17-10-1996	
٠.				EP	0830146	Α.	25-03-1998	
	÷			US	5762927	Α	09-06-1998	
WO	9953954	Α	28-10-1999	AU	3654499	A	08-11-1999	
WO	9856417		17-12-1998	 AU	7494098	Α	11-12-1998	
			•	AU	7956798	Α	30-12-1998	
				EP	0980259		23-02-2000	
	•			EP	1009432		21-06-2000	
				NO	995617		17-01-2000	
				WO	9852606	Α	26-11-1998	
WO	9839363	A	11-09-1998	AU	6542698	Α	22-09-1998	
				EP	1015496	Α	05-07-2000	
WO	9534320	Α	21-12-1995	AU	2701895	Α	05-01-1996	
			•	CA	2191733	Α	21-12-1995	
				EP	0784482		23-07-1997	
				JP	10501815	T	17-02-1998	



RECEIVED

APR 1 6 2001

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

McKEON, Tina W. NEEDLE & ROSENBERG, P.C. **Suite 1200** The Candler Building 127 Peachtree Street, N.E. Atlanta, GA 30303 **ETATS-UNIS D'AMERIQUE**

NEEDLE & ROSENBERG

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY **EXAMINATION REPORT**

(PCT Rule 71.1)

Date of mailing

(day/month/year)

09.04.2001

Applicant's or agent's file reference

14028.0293/P

IMPORTANT NOTIFICATION

International application No. PCT/US00/00284

International filing date (day/month/year) 06/01/2000

Priority date (day/month/year)

08/01/1999

Applicant

WISCONSIN ALUMNI RESEARCH FOUNDATION et al.

- 1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
- 2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
- 3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name / Date

JM

Name and mailing address of the IPEA/

European Patent Office D-80298 Munich

Tel. +49 89 2399 - 0 Tx: 523656 epmu d

Fax: +49 89 2399 - 4465

Hundt, D

Tel.+49 89 2399-8042

Authorized officer





PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applican	t's or a	gent's file reference				
14028.			FOR FURTHER ACTIO	A I	cation of Transmittal of Internati y Examination Report (Form PC	
Internation	nal ap	plication No.	International filing date (day/m	onth/year)	Priority date (day/month/yea	ır)
PCT/U	S00/0	0284	06/01/2000		08/01/1999	
A61K47	7/48	tent Classification (IPC) or nat				
WISCO	MOIN	ALUMNI RESEARCH I	FOUNDATION et al.			
		national preliminary exami namitted to the applicant ac	nation report has been prepactording to Article 36.	red by this Inte	ernational Preliminary Exam	ining Authority
2. This	REPO	ORT consists of a total of	8 sheets, including this cove	r sheet.		
	been a	amended and are the basi	by ANNEXES, i.e. sheets o s for this report and/or shee 7 of the Administrative Instru	s containing re	ctifications made before this	hich have s Authority
Thes	se ann	exes consist of a total of	sheets.			
3. This	report	contains indications relati	ing to the following items:			
ı	\boxtimes	Basis of the report				
II		Priority				
111	\boxtimes	Non-establishment of op	inion with regard to novelty,	inventive step a	and industrial applicability	
IV		Lack of unity of invention	1			
V	×	Reasoned statement und citations and explanation	der Article 35(2) with regard is suporting such statement	o novelty, inve	ntive step or industrial appli	cability;
VI		Certain documents cited	ľ			
VII	\boxtimes	Certain defects in the inte	ernational application			
VIII	×	Certain observations on t	the international application			
Date of sub	missio	n of the demand	Date	of completion of the	nis report	
07/08/20	00	:	09.04	2001		
	examir	address of the international ning authority:	Autho	rized officer		ESTO ASOES ANDING
<u>)</u>	D-80	oean Patent Office 298 Munich 49 89 2399 - 0 Tx: 523656 e	Boch	elen, D		With a state of the state of th
		+49 89 2399 - 4465	'	one No. ±49.89.3	2000 0450	KON THE THE WAY





International application No. PCT/US00/00284

ı	. в	asis of the report	
1	th a	ne receiving Office in	nents of the international application (Replacement sheets which have been furnished to response to an invitation under Article 14 are referred to in this report as "originally filed" this report since they do not contain amendments (Rules 70.16 and 70.17)):
	1.	-36	as originally filed
	С	laims, No.:	
	1-	33	as originally filed
2	. W laı	ith regard to the lang nguage in which the i	uage, all the elements marked above were available or furnished to this Authority in the nternational application was filed, unless otherwise indicated under this item.
	Th	ese elements were a	vailable or furnished to this Authority in the following language: , which is:
		the language of a t	ranslation furnished for the purposes of the international search (under Rule 23.1(b)).
			blication of the international application (under Rule 48.3(b)).
			ranslation furnished for the purposes of international preliminary examination (under Rule
3.	Wi	th regard to any nucl ernational preliminary	eotide and/or amino acid sequence disclosed in the international application, the examination was carried out on the basis of the sequence listing:
		contained in the inte	ernational application in written form.
			ne international application in computer readable form.
		furnished subseque	ently to this Authority in written form.
		furnished subseque	ently to this Authority in computer readable form.
			the subsequently furnished written sequence listing does not go beyond the disclosure in olication as filed has been furnished.
		The statement that slisting has been furn	the information recorded in computer readable form is identical to the written sequence nished.
4.	The	e amendments have r	esulted in the cancellation of:
		the description,	pages:
		the claims,	Nos.:
		the drawings,	sheets:
5.		This report has beer considered to go be	n established as if (some of) the amendments had not been made, since they have been yound the disclosure as filed (Rule 70.2(c)):



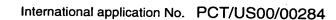


International application No. PCT/US00/00284

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

		report.)			
6	. Ad	ditional observations, if	necessa	ary:	
II	I. No	n-establishment of opi	inion w	ith regard	rd to novelty, inventive step and industrial applicability
1					on appears to be novel, to involve an inventive step (to be nonve not been examined in respect of:
		the entire international	applica	tion.	
	Ø	claims Nos. 1-33 with	respect	to industr	trial applicability.
be	ecau	se:			
	×				e said claims Nos. 1-33 relate to the following subject matter which ninary examination (<i>specify</i>):
		the description, claims that no meaningful opin			dicate particular elements below) or said claims Nos. are so unclear med (specify):
		the claims, or said clair could be formed.	ns Nos.	are so ir	inadequately supported by the description that no meaningful opinion
		no international search	report i	nas been	established for the said claims Nos
2.	and				nination cannot be carried out due to the failure of the nucleotide ly with the standard provided for in Annex C of the Administrative
		the written form has no	t been f	urnished	or does not comply with the standard.
		the computer readable	form ha	s not bee	en furnished or does not comply with the standard.
/ .		soned statement unde tions and explanations			with regard to novelty, inventive step or industrial applicability; ch statement
	State	ement			
	Nov	elty (N)	Yes: No:	Claims Claims	
	Inve	ntive step (IS)	Yes: No:	Claims Claims	
	Indu	etrial applicability (IA)	Voc	Claims	see separate sheet





No: Claims

2. Citations and explanations see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted: see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made: see separate sheet



INTERNATIONAL PRELIMINARY

International application No. PCT/US00/00284

EXAMINATION REPORT - SEPARATE SHEET

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: KOULMANDA M ET AL: 'Cyclophosphamide, but not CTLA4Ig, prolongs survival of fetal pig islet grafts in anti-T cell monoclonal antibody-treated NOD mice.' XENOTRANSPLANTATION (1998) 5 215-21 , XP000915296
- D2: WO 98 52606 A (BIOGEN) 26 November 1998 (1998-11-26)
- D3: WO 96 32137 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 17 October 1996 (1996-10-17)
- D4: WO 99 53954 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 28 October 1999 (1999-10-28)
- D5: WO 98 56417 A (THE UNITED STATES OF AMERICA) 17 December 1998 (1998-12-17)
- D6: WO 98 39363 A (THE GOVERNMENT OF THE UNITED STATES OF AMERICA) 11 September 1998 (1998-09-11)
- D7: WO 95 34320 A (REGENTS OF THE UNIVERSITY OF MINNESOTA) 21 December 1995 (1995-12-21)

2. Novelty (Art. 33 (1) and (2) PCT):

The prior art discloses methods to prevent graft rejection by using either inhibitors of T-cell co-stimulation, e.g. CTLA4-Ig (D1: p218 col1 §3; D5: p14 I21; D7: abstract,





INTERNATIONAL PRELIMINARY Inte

International application No. PCT/US00/00284

claim 7), 5c8 (D2: claim 5), anti-B7 antibody (D7: claim 8), or by reducing the T-cell population with immunotoxins (D3: claims 1, 7; D4: claims 1, 8; D6: claims 1, 27). Document D1 discloses the use of a combination of anti-CD3 or anti-CD4 antibodies and inhibitors of T cell co-stimulation (D1: p218 col2 §2) in order to prevent graft rejection. The subject-matter of claims 1-28 differs in that a combination of immunotoxins with inhibitors of the co-stimulation are proposed to prevent graft rejection. Therefore, the subject-matter of claims 1-28 appears to be new.

The subject-matter of **claims 29-33** is **considered to be new**. The prior art discloses the use of immunotoxins to induce immune tolerance by reducing T-cell population and thus to prevent acute graft rejection in the peritransplant period (D3: p18 I7; D4: p9 I10). The subject-matter of **claims 29-23** differs in that the immunotoxins are administered after transplantation when rejection occurs.

3. Inventive step (Art. 33 (1) and (3) PCT):

The subject-matter of claims 1-28 does not involve an inventive step for the following reasons.

Document D1, which is considered to be the closest prior art, discloses the combination of anti-CD3 or anti-CD4 antibodies that deplete the T-cell population (D1: abstract, p218 fig3), with an inhibitor of the co-stimulation of T-cells, i.e. CTLA4Ig, in order to prevent graft rejection. The problem underlying the application is therefore to find an alternative method to prevent graft rejection. The solution proposed is to combine co-stimulation blockers with immunotoxins. The prior art discloses the use of immunotoxins, e.g. UCHT1-CRM9 (D4: claim 8) in order to reduce the population of T-cells (D3: claim 1; D4: claim 1) and to prevent graft rejection. Therefore, it would be obvious for a man skilled in the art to use immunotoxins in combination with co-stimulation blockers in order to prevent graft rejection. Moreover, immunotoxins as well as co-stimulation blockers per se are known for their use to prevent graft rejection (see item 2.). The combination of known pharmaceutical compounds in order to obtain the same therapeutical effect as the compounds per se, involves an inventive step only if there is an unexpected advantage over the prior art. The application does not provide any evidence of such an advantage.

Immunotoxins are known for inducing immune tolerance by reducing T-cell



INTERNATIONAL PRELIMINARY

International application No. PCT/US00/00284

EXAMINATION REPORT - SEPARATE SHEET

population in the peritransplantation period (D3: p18 I7; D4: p9 I10) The subjectmatter of claims 29-33 differs in that immunotoxin treatment is administered when signs of rejection are detected. It would be obvious for a skilled man to administer the same treatment as used for inducing immune tolerance, in order to reverse the late acute graft rejection by reducing T-cell population. Therefore, the subject- matter of claims 29-33 does not involve an inventive step.

4. Industrial applicability (Art (1) and (4) PCT):

For the assessment of the present claims 1-33 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

- 5. The units of measure employed on page 17 are not additionally expressed in terms of the units stipulated by Rule 10.1 (a) PCT.
- 6. The units used on page 20 line 4 and page 24 line 9 are not consistent contrary to the requirement of Rule 10 (2) PCT.

Re Item VIII

Certain observations on the international application

- 7. The embodiment of the invention described on page 21 does not fall within the scope of the claims. This inconsistency between the claims and the description leads to doubt concerning the matter for which protection is sought, thereby rendering the claims unclear (Article 6 PCT).
- In claims 29-33, the step of monitoring the recipient for signs of rejection is not 8.



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considered to be a characterizing technical feature since it is a standard procedure following transplantation.

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